

Mercury Tissue Deposits: A New Adjuvant in Autoimmune/Inflammatory Syndrome

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Mercury exists as elemental mercury, inorganic salts or organic compounds. Elemental mercury is a heavy, silvery, shiny and liquid metal at room temperature. Toxicity depends on the type of mercury, route of exposure, load and rate of administration. The potential toxic effects of mercury depend on the route of exposure: a) intravenous administration of metallic mercury may produce embolization and death; b) inhalation of mercury vapor may cause weakness, fever, respiratory failure and death; c) subcutaneous mercury injection may lead to inflammatory soft tissue lesions and abscesses associated with fever; d) the oral route is rarely of clinical significance.

The skin lesions associated with subcutaneous mercury injections include skin abscesses, foreign body giant cell reaction, lichenoid papules due to dental amalgams or drugs, reaction to tattoo, mercury exanthema, cutaneous hyperpigmentation, and contact dermatitis. Other important manifestations of mercury toxicity are psychiatric symptoms; these seem to result from a dysregulation of the posterior cingulate cortex which is associated with attention/concentration deficits and marked anxiety/agitation.

Adjuvants have been associated with defined and non-defined immune mediated diseases in both animal models and humans. Clinically, they share a similar complex of signs and symptoms that further support a common denominator known as ASIA (autoimmune/inflammatory syndrome induced by adjuvants). Mercury has also been associated with autoantibody production and immune complex-mediated tissue injury and could be an adjuvant related to ASIA. The case presented here suggests that mercury could act as an adjuvant in predisposed patients [1,2].

PATIENT DESCRIPTION

A 30 year old woman with a history of foreign elements in her body was admitted to our hospital. She had had two dental amalgams inserted 10 years earlier, 4 large tattoos applied 8 years before admission, and one year prior to admission she was injected with an unknown liquid in her abdominal subcutaneous region.

Ten months before admission she had intermittent fever up to 39°C and 20 kg weight loss. Six months prior to admission to our hospital, she was admitted to another hospital following the appearance of painful macules, which were wine-colored and rapidly progressive, appearing first on the skin of the left breast and rapidly spreading to the contralateral breast. Fine-needle aspiration cytology of these palpable breast lesions revealed two groups of cells with cytologic atypia. The intraoperative biopsy suggested low grade angio-

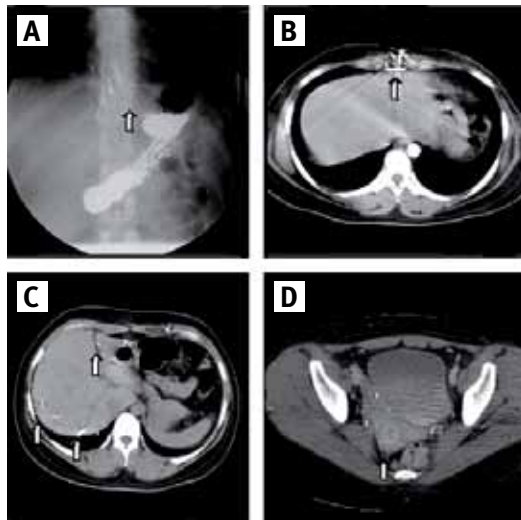
sarcoma and a bilateral mastectomy was performed [Figure 1A]. The final histological diagnosis was angiomatosis, sclerosing adenosis and purulent mastitis secondary to foreign body reaction. Sixteen lymph nodes showed angiomatosis and mixed hyperplasia.

Following mastectomy, the fever, fatigue and weakness persisted, leading to an exhaustive 3 month search for viral, bacterial and fungal infection, but infection was ruled out. In addition to the fever, she complained of decreased appetite, impaired concentration and memory, myalgia, arthralgia, headache and excessive fatigue, sleepiness, anxiety and depression. Hence, we decided that our approach to the clinical investigation would be appropriate to “fever of unknown origin.” One important sign was the intermittent appearance of vinous, very painful palpable lesions, similar to the ones present before mastectomy, varying from 1 to 10 cm with irregular borders. These lesions were located on the face, neck, anterior chest and limbs, lasted 15 to 20 days and disappeared completely. Laboratory results were as follows: creatinine 0.78 mg/dl, total proteins 6.7 g/dl, albumin 4.1 g/dl, total bilirubin 0.7 mg/dl, and normal serum electrolytes and liver function tests. White blood cells were 7200/mm³ (56.1% neutrophils), hemoglobin 11.9 g/dl, platelets 384,000/mm³, prothrombin time 13 sec and activated partial thromboplastin time 29.7 sec. Platelet aggregation tests showed ADP-induced platelet aggregation 86%, epinephrine-induced platelet aggregation 66%, and thrombin-induced platelet aggregation 81%. Immunoglobulin G was 1170

Figure 1. [A] Mastectomy scars still in the healing phase. New angiomatosis lesions located in the lower left thoracic region. [B] Elemental mercury before removal from the subcutaneous tissue in the epigastric region. [C] Mercury extracted as a liquid elemental metal



Figure 2. Elemental mercury distributed in different locations (arrow). [A] Esophagogram showing opacities outside the digestive tract. [B] Hyperdensities and Hounsfield effect within abdominal subcutaneous tissue. [C] Mercury deposits in liver parenchyma. [D] Mercury deposits in soft tissues in the pelvic cavity



mg/dl, IgA 375 mg/dl, IgM 150 mg/dl, C3 153 mg/dl, C4 35.7 mg/dl, and C-reactive protein 13.1 mg/L. Immunological analysis showed intermittent positive autoantibodies: antinuclear antibodies 1:80 fine speckled pattern, anti-dsDNA 920 IU/ml, antimitochondrial 1:80, and p-ANCA 1:20 in the absence of vasculitis or other autoimmune specific disease.

Among the examinations the esophagogram showed diffuse opacities in the upper abdomen outside the esophagus [Figure 2A]. A thoracoabdominal tomographic examination showed hyperdensities ~1000 Hounsfield units from 3 to 20 mm, located in the subcutaneous abdominal fat and liver, kidneys and pelvis [Figure 2B and C]. A cranial tomography examination revealed a 3 cm diameter frontal calcification.

Later, a surgical excision of abdominal fat showed that the hyperdensities previously mentioned corresponded to deposits of elemental mercury [Figure 1B and C]. A biopsy of tissue around the mercury showed mixed panniculitis (globular and septal) and foreign body-type multinucleated giant cells without vasculitis [Figure 3A and B]. The biopsy of red and black tattoos was normal. In a second procedure, 5 ml of elemental mercury was extracted from the subcutaneous abdominal fat by ultrasonography-guided puncture. Mercury concentrations in blood and urine were normal (< 10 µg/L) on the first examination but increased 1 month later (blood 14.0 µg/L and urine 11.2 µg/L).

The patient met six of the seven major criteria for ASIA: fever, myalgia, weakness,

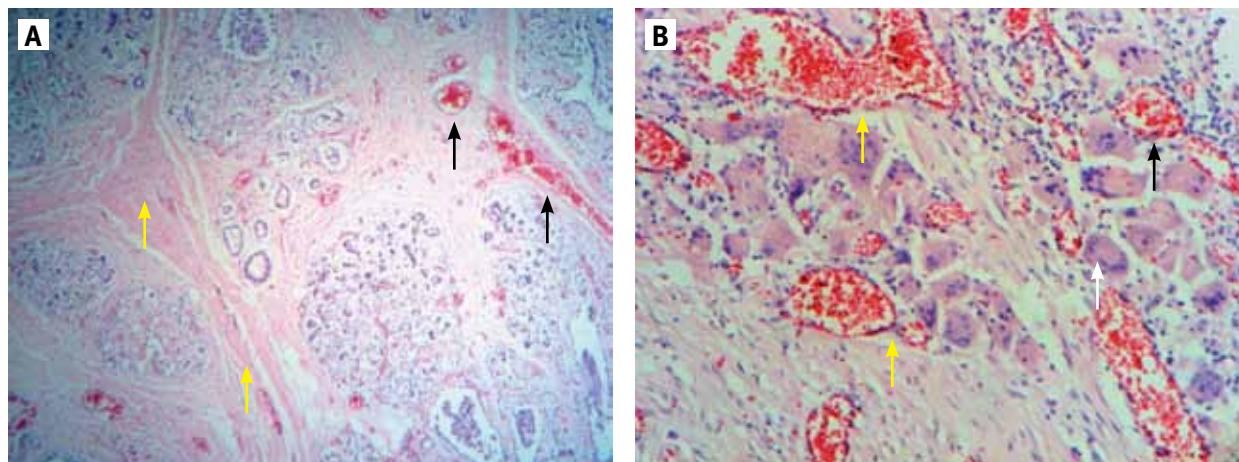
arthralgia, sleepiness, impaired concentration and memory in association with an adjuvant (mercury), and granulomas by histological analysis. A minor criterion was the presence of autoantibodies. She was treated with penicillamine, clonazepam, dextropropoxyphene, citalopram and paracetamol. After one month of treatment with penicillamine 300 mg orally three times a day, the fever subsided, but the skin lesions, general symptoms persisted until the present time due to the difficulty of removing the mercury in its entirety.

COMMENT

We describe a patient whose condition first manifested with persistent fever, non-specific rheumatic disease features, angiomatosis and purulent mastitis associated with a foreign body. She was treated with bilateral mastectomy due to the histological possibility of malignancy. Several months later, these manifestations were associated with mixed panniculitis and the presence of nucleated giant cells. Mercury deposits acted as a foreign body and were associated with serum expression of autoantibodies. Psychiatric manifestations, fatigue and sleep disorders were additional relevant symptoms. We propose this case as an autoimmune/inflammatory syndrome induced by adjuvants, the adjuvant being mercury.

The tissue reaction following subcutaneous mercury injection includes early and late reaction patterns. Early reactions include necrosis, acute inflammatory reac-

Figure 3. Histological changes of angiomatosis and panniculitis. **[A]** Breast tissue with angiomatosis and fibrosis. **[B]** Fat tissue near mercury deposits: lymphocytic infiltration (black arrow), foreign body-type multinucleated giant cell (white arrow) and vascular proliferation (yellow arrow)



tions and aseptic abscess formation. Late reactions include foreign-body giant cell reaction, fibrosis, granuloma formation and membranous fat necrosis. Our patient initially had purulent mastitis secondary to a foreign body as an early reaction and, months later, a mixed panniculitis with nucleated giant cells as a late reaction to the foreign body. In addition, she had angiomatosis in both breasts and hyperplasia plus angiomatosis in 16 lymph nodes.

Angiomatosis is defined as “a diseased state of the vessels with the formation of multiple angiomas”; however, when blood-filled vessels are also present in the lymph nodes it is more difficult to distinguish them from vascular tumors [3]. These vascular (capillary) proliferations in the skin present clinically as multiple erythematous-violaceous and purpuric patches and plaques, sometimes with necrosis and ulceration. Histologically, they are characterized by intravascular or extravascular, lobular or diffuse hyperplasia of endothelial cells, pericytes, or histiocytes that can mimic vascular tumors due to unusual cytological atypia and atypical mitoses in the endothelial cells. These histological characteristics are reactive in that they seem to originate from the occlusion of a vascular lumen. Vascular proliferation stops after the inducing hypoxic stimulus has been withdrawn [3,4].

In our patient, the cytological atypia and atypical mitoses observed intraoperatively suggested vascular malignancy. The rapid progression of these lesions prompted the bilateral mastectomy. Angiomas are infrequent and has never been reported in the literature in association with mercury deposits. We think it likely that the mercury was transported through the blood circulation, causing temporary obstruction of small vessels. Therefore, this obstruction might have produced a distal hypoxic stimulus that could explain the appearance of angiomas in distant locations from larger mercury deposits. In support of this, the blood and urine mercury concentrations fluctuated from normal to toxic levels.

When liquid metal mercury is injected subcutaneously it can cause a local reaction, but the slow absorption may not produce an acute toxic effect. It is important to extract the mercury and to monitor the central nervous system and renal function. The evidence of systemic toxicity requires chelation therapy. In the present case, total extraction was not possible due to the wide distribution in the liver, kidney and pelvis. The only feasible site for extraction was the subcutaneous abdominal fat. Chelation therapy was necessary, although insufficient.

The evidence that mercury can induce gene-controlled autoimmunity in both

humans and animal models is old [2]. This case was positive for diverse autoantibodies without a specific autoimmune disease. The risk for this patient developing an autoimmune disease in the future is high.

Recently, Agmon-Levin et al. [5] described a syndrome, which they termed ASIA – autoimmune/inflammatory syndrome induced by adjuvants – characterized by a similar complex of signs and symptoms in response to hyperactive immunity and manifested as an autoimmune or autoinflammatory disease. The use of medical adjuvants has become common practice and substances such as aluminum adjuvant are added to most vaccines. The spectrum of histological reaction following vaccination or allergen desensitization shows histiocytes with violaceous granular cytoplasm. The overlapping patterns of focal fibrosis, fat necrosis and a mixed inflammatory cell infiltrate mainly in the subcutis gives rise to the features of a non-specific septal and lobular panniculitis. Histological changes in tissues adjacent to the area of surgical removal of mercury were similar to those reported with aluminum. The histological changes in this case and the previously described clinical manifestations are compatible with the ASIA syndrome.

We conclude that this case of angiomas, persistent fever and non-specific

rheumatic and psychiatric manifestations associated with mercury deposits meets the criteria for ASIA syndrome. The removal of mercury is the mandatory treatment in these cases, although in this patient it was not possible due to the extensive tissue distribution. The presence of diverse autoantibodies in this patient mandates close follow-up to detect the appearance of an autoimmune disease in the future. It is important to consider the impact of mercury as an environmental

factor of high risk in the development of autoimmune/autoinflammatory disease.

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References

1. Shoenfeld Y, Agmon-Levin N. ASIA – autoimmune/inflammatory syndrome induced by adjuvant. *J Autoimmun* 2011; 36: 4-8.
2. Druet PH. Metal-induced autoimmunity. *Hum Exp Toxicol* 1995; 14: 120-1.
3. Mitsuhashi T, Hirose T, Kuramochi A, Tsuchida T, Shimizu M. Cutaneous reactive angiomatosis occurring in erythema ab igne can cause atypia in endothelial cells: potential mimic of malignant vascular neoplasm. *Pathol Int* 2005; 55: 431-5.
4. Rongioletti F, Rebora A. Cutaneous reactive angiomatosis: patterns and classification of reactive vascular proliferation. *J Am Acad Dermatol* 2003; 49: 887-96.
5. Agmon-Levin N, Hughes GRV, Shoenfeld Y. The spectrum of ASIA: 'Autoimmune (Auto-inflammatory) Syndrome induced by Adjuvants'. *Lupus* 2012; 21: 118-20.

Capsule

Limited airborne transmission of H7N9 influenza A virus between ferrets

Wild waterfowl form the main reservoir of influenza A viruses, from which transmission occurs directly or indirectly to various secondary hosts, including humans. Direct avian-to-human transmission has been observed for viruses of subtypes A(H5N1), A(H7N2), A(H7N3), A(H7N7), A(H9N2) and A(H10N7) upon human exposure to poultry, but a lack of sustained human-to-human transmission has prevented these viruses from causing new pandemics. Recently, avian A(H7N9) viruses were transmitted to humans, causing severe respiratory disease and deaths in China. Because transmission via respiratory droplets and aerosols (hereafter referred to as airborne transmission) is the main route for efficient transmission between humans, it is important to gain an insight into airborne transmission of the A(H7N9)

virus. Richard et al. show that although the A/Anhui/1/2013 A(H7N9) virus harbors determinants associated with human adaptation and transmissibility among mammals, its airborne transmissibility in ferrets is limited, and it is intermediate between that of typical human and avian influenza viruses. Multiple A(H7N9) virus genetic variants were transmitted. Upon ferret passage, variants with higher avian receptor binding, higher pH of fusion, and lower thermostability were selected, potentially resulting in reduced transmissibility. This A(H7N9) virus outbreak highlights the need for increased understanding of the determinants of efficient airborne transmission of avian influenza viruses among mammals.

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Eitan Israeli

Capsule

Cross-neutralization of four paramyxoviruses by a human monoclonal antibody

Broadly neutralizing antibodies reactive against most and even all variants of the same viral species have been described for influenza and HIV-1. However, whether a neutralizing antibody could have the breadth of range to target different viral species was unknown. Human respiratory syncytial virus (HRSV) and human metapneumovirus (HMPV) are common pathogens that cause severe disease in premature newborns, hospitalized children and immune-compromised patients, and play a role in asthma exacerbations. Although antisera generated against either HRSV or HMPV are not cross-neutralizing, Corti et al. speculated that, because of the repeated exposure to these viruses, cross-neutralizing antibodies may be selected in some individuals. Now they describe a human monoclonal antibody (MPE8) that potently cross-neutralizes HRSV and HMPV as well as two animal paramyxoviruses: bovine RSV (BRSV) and pneumonia virus of mice (PVM). In its germline configuration, MPE8 is HRSV-

specific and its breadth is achieved by somatic mutations in the light chain variable region. MPE8 did not result in the selection of viral escape mutants that evaded antibody targeting and showed potent prophylactic efficacy in animal models of HRSV and HMPV infection, as well as prophylactic and therapeutic efficacy in the more relevant model of lethal PVM infection. The core epitope of MPE8 was mapped on two highly conserved anti-parallel β -strands on the pre-fusion F protein, which are rearranged in the post-fusion F protein conformation. Twenty-six of the 30 HRSV-specific neutralizing antibodies isolated were also found to be specific for the pre-fusion F protein. Taken together, these results indicate that MPE8 might be used for the prophylaxis and therapy of severe HRSV and HMPV infections and identify the pre-fusion F protein as a candidate HRSV vaccine.

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